Complete Summary

GUIDELINE TITLE

Pharmacology and management of the vitamin K antagonists. American College of Chest Physicians evidence-based clinical practice guidelines (8th edition).

BIBLIOGRAPHIC SOURCE(S)

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):160S-98S. [419 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):204S-33S.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 3, 2008, Innohep (tinzaparin): The U.S. Food and Drug Administration (FDA) has requested that the labeling for Innohep be revised to better describe overall study results which suggest that, when compared to unfractionated heparin, Innohep increases the risk of death for elderly patients (i.e., 70 years of age and older) with renal insufficiency. Healthcare professionals should consider the use of alternative treatments to Innohep when treating elderly patients over 70 years of age with renal insufficiency and deep vein thrombosis (DVT), pulmonary embolism (PE), or both.
- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with

symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Thromboembolic disorders including the following:

- Primary and secondary venous thromboembolism
- Systemic embolism
- Myocardial infarction

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Emergency Medicine
Family Practice
Hematology
Internal Medicine
Neurology
Oncology
Orthopedic Surgery
Pharmacology
Surgery

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Patients
Pharmacists
Physicians
Psychologists/Non-physician Behavioral Health Clinicians
Social Workers

GUIDELINE OBJECTIVE(S)

- To describe the antithrombotic effects of vitamin K antagonists (VKAs), the monitoring of anticoagulation intensity, and the clinical applications of VKA therapy and provide specific management recommendations
- To update evidence-based recommendations for the use of VKAs for the management of thromboembolic conditions

TARGET POPULATION

Patients requiring oral anticoagulant therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Vitamin K antagonists (VKAs)*
2. Heparin or low-molecular-weight heparin (LMWH)
3. Reversal of VKAs:
    - Vitamin K
    - Fresh frozen plasma
    - Prothrombin complex concentrate (PCC)
    - Recombinant factor VIIa

*__Note__: Since warfarin is the most commonly used VKA worldwide, warfarin was used interchangeably with VKA or coumarin.

Management

1. Systematic and coordinated approach
2. Prothrombin time (PT) monitoring
3. Systematic international normalized ratio (INR) monitoring
4. Patient education
5. Good patient communication of results and dosing decisions
6. Follow-up

MAJOR OUTCOMES CONSIDERED

- Incidence of thrombosis
- Recurrent thromboembolism
- Incidence of major and minor hemorrhage

- Time to achieve therapeutic international normalized ratio (INR)
- Anticoagulant response
- Maintenance dose
- Time in the therapeutic range (TTR)
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Process of Searching for Evidence

Defining the clinical question provided the framework for formulating eligibility criteria that guided the search for relevant evidence. In specifying eligibility criteria, authors identified not only patients, interventions, and outcomes, but also methodologic criteria. For many recommendations, authors restricted eligibility to randomized controlled trials (RCTs).

For many questions, randomized trials did not provide sufficient data, and chapter authors included observational studies when randomized trials were not the most appropriate design to address the research question. In particular, randomized trials are not necessarily the best design to understand risk groups, that is, the baseline or expected risk of a given event for certain subpopulations. Because no interventions are typically examined in questions about prognosis, one replaces interventions by the duration of exposure measured in time.

Identifying the Evidence

To identify the relevant evidence, a team of librarians and research associates at the McMaster University Evidence based practice center (EPC) conducted comprehensive literature searches. Methodologic experts (including the editors) and the EPC librarians reviewed each question to ensure the development of a comprehensive search strategy. For example, for questions about antiplatelet agents, the EPC consulted chapter authors to ensure that the search included all relevant antiplatelet agents. More specifically, authors then decided whether to include dipyridamole in a search that already included aspirin, clopidogrel, and ticlopidine.

For each question the authors provided, the librarians searched the Cochrane Database of Systematic Reviews, MEDLINE, and Embase for published English-language literature and human studies between 2002 and May 2006. To filter MEDLINE and Embase search results for RCT evidence, the librarians used the search strategy developed by the Cochrane Collaboration. These searches updated the more comprehensive and sensitive searches conducted for the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines.

The EPC team conducted separate searches for systematic reviews; RCTs; and, if applicable, observational studies. For observational studies, searches were not restricted in terms of methodology. Although increasing the probability of identifying all published studies, this sensitive approach resulted in large numbers of citations for many of the defined clinical questions. Therefore, trained research assistants screened the citation list developed from the search using criteria of increased specificity to reduce the number of irrelevant citations that the authors received. These irrelevant citations included press news, editorials, narrative reviews, single-case reports, studies that included fewer participants than specified by authors as an inclusion criterion, animal studies (any nonhuman studies), and letters to the editor. Authors did not include data from abstracts of meetings for the development of recommendations, and the guideline developers did not explicitly use Internet sources to search for research data. Authors were encouraged, however, to mention abstracts that reported on groundbreaking data that were particularly relevant to a specific question in the chapters in order to alert readers that new, fully published evidence might become available shortly.

Standard Consideration of Study Quality

High-quality clinical guidelines should pay careful attention to the methodologic quality of the studies that form the basis of their recommendations. Using the example of the prevention of venous thromboembolism during air travel, Table 1 in the methodology companion (see "Availability of Companion Documents" field) shows the criteria for assessment of study quality (randomization, concealment or treatment allocation, blinding, completeness of follow-up, and whether the analysis was performed according to the intention-to-treat principle), and Table 2 in the methodology companion (see "Availability of Companion Documents" field) shows the presentation of results that were circulated to the authors. Whereas all authors attended to these criteria, the guideline developers have summarized the results of the quality assessment for only a minority of the recommendations. Readers can find these summaries in an online appendix to the recommendations (see online supplemental data).

In assessing the quality of observational studies, the guideline developers did not make a distinction between prospective and retrospective because the key issues are unbiased sampling, high-quality measurement of patient characteristics and outcomes, and complete follow-up.

Although it is more likely that these quality criteria will be achieved in prospective studies, prospective studies may fail to achieve them, and retrospective studies may succeed. The guideline developers did make a key distinction about whether internal comparisons exist and their nature. Studies without internal comparisons received the label "case series" unless they met the following criteria: (1) a protocol existed before the date of commencement of data collection; (2) a definition of inclusion and exclusion criteria was available; (3) the study reported the number of excluded patients; (4) the study conducted a standardized follow-up, including description of schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes; and (5) the study reported all losses to follow-up.

The guideline developers labeled studies that met these criteria "cohort studies without internal controls." Studies with internal comparisons received the label

"cohort studies with concurrent controls" or "cohort studies with historical controls." These cohort studies may succeed or fail to ensure settings, similar time frames, adjustment for differences in patients' characteristics, and follow-up with patients. These features were captured in descriptive tables provided to authors when requested from the EPC.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scheme framework captures the trade-off between benefits and risks (1 or 2) and the methodological quality of the underlying evidence (A, B, or C). See "Grades of recommendations for antithrombotic agents" in the "Availability of Companion Documents" field and the "Rating Scheme for the Strength of the Recommendations." field.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Summarizing Evidence

The electronic searches also included searches for systematic reviews. If authors were satisfied with a recent high-quality systematic review, evidence from that review provided a foundation for the relevant recommendation.

Pooled analyses from high-quality systematic reviews formed summary data on which panelists based their recommendations wherever possible. Pooling offers the advantage of obtaining more precise estimates of treatment effects and allows for greater generalizability of results. However, pooling also bears the risk of spurious generalization. In general, the summary estimates of interest were the different types of outcomes conveying benefits and downsides (risk, burden, and cost). When pooled estimates of effects were not available, the McMaster University Evidence based practice center (EPC) conducted meta-analysis to obtain pooled estimates for specific questions. These were questions that authors had specifically identified.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Group-Specific Recommendations

In general, the guideline developers have endeavored to make their recommendations as specific as possible for patient subgroups differing according to risk. Whenever valid prognostic data were available, the guideline developers used them to estimate absolute effects and made recommendations accordingly. Unfortunately, reliable prognostic indexes are not usually available, limiting the extent to which such group-specific recommendations are possible.

Acknowledge Values and Preferences and Resource Use Underlying Recommendations

Under ideal circumstances, knowledge of average patient values and preferences would be available for every recommendation, the panel members would summarize these values and preferences, and they would be integrated into the recommendations that guideline developers make. The guideline developers asked all chapter chairs before beginning the searches for the relevant literature to identify recommendations that they believed were particularly sensitive to patients' values and preferences. Moderate-quality evidence regarding values and preferences bearing directly on the recommendations proved available for only the chapter that addresses antithrombotic therapy in patients with atrial fibrillation. The panelists bore in mind what average patient values and preferences may be; the process, however, is speculative.

The guideline developer's main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation.

In addition, the guideline developers involved three consultants with expertise in the area of values and preferences to collaborate with the chairs of two chapters and try to ensure that the guidelines adequately represented the views of patients. This collaboration led to extensive discussions among the chapter authors and the consultants and the reflection of these discussions in the associated values and preference statements.

Finalizing and Harmonizing Recommendations

After having completed the steps the guideline developers have described above, the guideline authors formulated draft recommendations before the conference, which laid the foundation for authors to work together and critique the recommendations. Figure 1 in the methodology companion (see "Availability of Companion Documents" field) shows the process of guideline development and review. Drafts of chapters that included draft recommendations were usually distributed for peer review to at least two panel members and were always reviewed by at least one panel editor before the conference. Written critiques were prepared and returned to the authors for revision of their work. At the plenary conference, a representative of each chapter presented potentially controversial issues in their recommendations. Chapter authors met to integrate

feedback and consider related recommendations in other chapters and to revise their own guidelines accordingly. Authors continued this process after the conference until they reached agreement within their groups and with other author groups who provided critical feedback. The editors of this supplement harmonized the chapters and resolved remaining disagreements between chapters through facilitated discussion. All major correspondence and discussions at the meeting were recorded in written and audio protocols and are publicly available.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence,	Desirable effects closely	Consistent evidence from RCTs without important	The best action may differ depending on circumstances or patient

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Grade 2A	balanced with undesirable effects	limitations or exceptionally strong evidence from observational studies	or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

*The guideline developers use the wording *recommend* for strong (Grade 1) recommendations and *suggest* for weak (Grade 2) recommendations.

COST ANALYSIS

For these guidelines, the guideline developers implemented recommendations of a recent American College of Chest Physicians (ACCP) task force on integrating resource allocation in clinical practice guidelines by restricting resource expenditure consideration to a small number of recommendations for which they were particularly relevant. The guideline developers relied on two consultants with expertise in economic assessment to help with the process of considering costs in those small numbers of recommendations that guideline developers considered very important to the decision.

Recommendations highly sensitive to resource allocation now include value and preference statements regarding how cost issues were integrated.

Refer to "Strategies for incorporating resource allocation and economic considerations" (see "Availability of Companion Documents" field) for details of the cost analyses.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The American College of Chest Physicians (ACCP) Health Science Policy (HSP) established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the editors, the guidelines underwent review by appropriate NetWorks of the ACCP (for these guidelines, the Cardiovascular and Pulmonary Vascular NetWorks), the HSP, and the Board of Regents. The latter two have the right of approval or disapproval but usually work with the guideline authors and editors to make necessary revisions before final approval. Each group identified primary reviewers who read the full set of chapters as well as individual committee members who were responsible for reviewing one or more chapters. The reviewers considered both content and methodology as well as whether there was balanced, not biased, reporting and adherence to HSP processes. Finally, the *CHEST* editor-in-chief read and forwarded the manuscripts for nonbiased, independent, external peer review before acceptance for publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) are defined at the end of the "Major Recommendations" field.

Please refer to the original full-length guideline document for a detailed description of the pharmacology and monitoring of vitamin K antagonists (VKAs), the pharmacokinetics and pharmacodynamics of warfarin (including genetic and environmental factors), the antithrombotics effect of VKAs, monitoring anticoagulation intensity, and clinical applications of VKA therapy.

Initiation and Maintenance Dosing

In patients beginning vitamin K antagonist (VKA), therapy, we recommend the initiation of oral anticoagulation with doses between 5 mg and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the international normalized ratio (INR) response **(Grade 1B)**. At the present time, for patients beginning VKA therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing **(Grade 2C)**

Initiation of Anticoagulation in the Elderly or Other Populations

In elderly patients or patients who are debilitated, are malnourished, have congestive heart failure, have liver disease, have had recent major surgery, or are taking medications known to increase the sensitivity to warfarin (e.g., amiodarone), we recommend the use of a starting dose of $\leq$5 mg **(Grade 1C)** with subsequent dosing based on the international normalized ratio (INR) response.

Frequency of Monitoring

1. In patients beginning VKA therapy, we suggest that INR monitoring should be started after the initial two or three doses of oral anticoagulation therapy **(Grade 2C)**.
2. For patients who are receiving a stable dose of oral anticoagulants, we suggest monitoring at an interval of no longer than every 4 weeks **(Grade 2C)**.

Management of Nontherapeutic INRs

1. For patients with INRs above the therapeutic range, but < 5.0 and with no significant bleeding, we recommend lowering the dose or omitting a dose, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level. If only minimally above therapeutic range, or associated with a transient causative factor, no dose reduction may be required **(all Grade 1C)**.
2. For patients with INRs $\geq$5.0 but <9.0 and no significant bleeding, we recommend omitting the next one or two doses, monitoring more frequently, and resuming therapy at an appropriately adjusted dose when the INR is at a therapeutic level **(Grade 1C)**. Alternatively, we suggest omitting a dose and administering vitamin K (1 to 2.5 mg) orally, particularly if the patient is at increased risk of bleeding **(Grade 2A)**. If more rapid reversal is required because the patient requires urgent surgery, we suggest vitamin K ($\leq$5 mg) orally, with the expectation that a reduction of the INR will occur in 24 hours. If the INR is still high, we suggest additional vitamin K (1 to 2 mg) orally **(Grade 2C)**.
3. For patients with INRs of ≥ 9.0 and no significant bleeding, we recommend holding warfarin therapy and administering a higher dose of vitamin K (2.5 to 5 mg) orally, with the expectation that the INR will be reduced substantially in 24 to 48 hours **(Grade 1B)**. Clinicians should monitor the INR more frequently, administer additional vitamin K if necessary, and resume therapy at an appropriately adjusted dose when the INR reaches the therapeutic range.
4. In patients with serious bleeding and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and giving vitamin K (10 mg) by slow IV infusion supplemented with fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation. We recommend repeating vitamin K administration every 12 hours for persistent INR elevation **(All Grade 1C)**.
5. In patients with life-threatening bleeding (e.g., intracranial hemorrhage) and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and administering fresh frozen plasma, prothrombin complex concentrate (PCC), or recombinant factor VIIa supplemented with

vitamin K, 10 mg by slow IV infusion, repeated, if necessary, depending on the INR **(Grade 1C)**.

6. In patients with mild-to-moderately elevated INRs without major bleeding, we recommend that when vitamin K is to be given, it be administered orally rather than subcutaneously **(Grade 1A)**.

Management of Variable INRs

For patients receiving long-term warfarin therapy with a variable INR response not attributable to any of the usual known causes for instability, we suggest a trial of daily low-dose oral vitamin K (100 to 200 microgram) with close monitoring of the INR and warfarin dose adjustment to counter an initial lowering of the INR in response to vitamin K **(Grade 2B)**.

Management of INRs in Antiphospholipid Syndrome

In patients who have a lupus inhibitor, who have no additional risk factors, and no lack of response to therapy, we recommend a therapeutic target INR of 2.5 (INR range, 2.0 to 3.0) **(Grade 1A)**. In patients who have recurrent thromboembolic events with a therapeutic INR or other additional risk factors for thromboembolic events, we suggest a target INR of 3.0 (INR range, 2.5 to 3.5) **(Grade 2C)**.

Optimal Management of VKA Therapy

For health-care providers who manage oral anticoagulation therapy, we recommend that they do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions as occurs in an anticoagulation management service **(Grade 1B)**.

Patient Self-Testing and Patient Self-Management

Patient self-management is a choice made by patients and health-care providers that depends on many factors. In patients who are suitably selected and trained, patient self-testing and patient self-management is an effective alternative treatment model. We suggest that such therapeutic management be implemented where suitable **(Grade 2B)**.

Definitions:

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Strong recommendation, high-quality evidence, Grade 1A	Desirable effects clearly outweigh	Consistent evidence from RCTs without important limitations or	Recommendation can apply to most patients in most circumstances; further research is very

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
	undesirable effects, or *vice versa*	exceptionally strong evidence from observational studies	unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low or very low-quality evidence, Grade 1C	Desirable effects clearly outweigh undesirable effects, or *vice versa*	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values; higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Grading Recommendation			
Grade of Recommendation*	**Benefit vs. Risk and Burdens**	**Methodologic Quality of Supporting Evidence**	**Implications**
Weak recommendation, low or very low-quality evidence, Grade 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate

*The guideline developers use the wording *recommend* for strong (Grade 1) recommendations and *suggest* for weak (Grade 2) recommendations.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate monitoring and management of patients who require treatment with vitamin K antagonists (VKAs)

POTENTIAL HARMS

- Refer to Table 2 of the original guideline document entitled "Drug and Food Interactions with Warfarin by Level of Supporting Evidence and Direction of Interaction" for information on potentiation, inhibition, and no effect interactions.
- Refer to Table 3 of the original guideline document entitled "Potential Problems with International Normalized Ratio (INR) (Causes of Erroneous INR)" for information on problems with INR monitoring.
- Vitamin K antagonists are associated with minor and major hemorrhagic events.
- High doses of vitamin K, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for a week or more.

- Intravenous (IV) injection of vitamin K may be associated with anaphylactic reactions, although such reactions have even been described with non-IV routes of administration.
- Other than hemorrhage, the most important side effects of warfarin are acute thrombotic complications, such as skin necrosis and limb gangrene. These uncommon complications are usually observed on the third to eighth day of therapy and are caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat (in the case of skin necrosis) and massive outflow obstruction of the venous circulation of the limb (in the case of limb gangrene).

Refer to Tables 6, 7, and 8 of the original guideline document for information on the frequency of major hemorrhage/thromboembolism in patients managed under an anticoagulation management service (AMS), the frequency of major hemorrhage/thromboembolism in patients managed under usual care vs. AMS, and the frequency of major hemorrhage/thromboembolism in patients self-managed vs. usual care or AMS, respectively.

Subgroups Most Likely to Experience Harms

Several patient characteristics have been shown to be associated with higher odds of bleeding during anticoagulation therapy. The patient factor that most consistently has been demonstrated to be predictive of major bleeding is a history of bleeding (especially gastrointestinal [GI] bleeding). Other factors associated with a higher risk of bleeding include a history of stroke and the presence of a serious comorbid condition such as renal insufficiency, anemia, or hypertension.

CONTRAINDICATIONS

CONTRAINDICATIONS

The management of patients with warfarin-induced skin necrosis who require lifelong anticoagulant therapy is problematic. Therapy with warfarin is considered to be contraindicated, and long-term heparin therapy is inconvenient and is associated with osteoporosis.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Limitations of These Guideline Development Methods

Limitations of these guidelines include the limited quantity and quality of available studies for some patient groups. Second, it is possible that some authors followed this methodology more closely than others, although the development process was centralized by an evidence-based practice center (EPC) and supervised by the editors. Third, it is possible that the guideline developers missed relevant studies in spite of the comprehensive searching process. Fourth, despite their efforts to begin centralizing the methodologic evaluation of all studies to facilitate uniformity in the validity assessments of the research incorporated into these guidelines,

resources were insufficient to conduct this evaluation for all but a few of the recommendations in each chapter. Fifth, the guideline developers performed only few statistical pooling exercises of primary study results. Finally, sparse data on patient preferences and values represent additional limitations inherent to most guideline development methods.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy includes local educational programs and tools offered through the American College of Chest Physicians (ACCP) Board of Governors and select other locations. The Veterans Administration (VA) will also participate in a pilot project.

IMPLEMENTATION TOOLS

Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):160S-98S. [419 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Sep (revised 2008 Jun)

GUIDELINE DEVELOPER(S)

American College of Chest Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Chest Physicians

GUIDELINE COMMITTEE

American College of Chest Physicians (ACCP) Expert Panel on Antithrombotic and Thrombolytic Therapy

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Ansell discloses that he has received consultant fees from Bristol-Myers Squibb, Roche Diagnostics, and International Technidyne Corporation. He is also on the speakers bureau for Roche Diagnostic Corporation and Sanofi-Aventis, and is the past president of the Anticoagulation Forum.

Dr. Hirsh discloses that he has received partial support for writing two books, one on fondaparinux and one on low-molecular-weight heparin.

Dr. Jacobson discloses that he has received grant monies from the National Institutes of Health, the Department of Veterans Affairs, Sanofi, Boehringer Ingelheim, and Roche Diagnostics. He is on the speakers bureau for Bristol-Myers Squibb and GlaxoSmithKline. Dr. Jacobson has served on advisory committees for Roche Diagnostics and Sanofi. He has served in fiduciary positions for the Loma Linda Veterans Association for Research and Education, the Loma Linda University School of Medicine Alumni Association, and the Anticoagulation Forum.

Dr. Hylek discloses that she has received grant monies from AstraZeneca and Bristol-Myers Squibb, and that she has also served on an advisory committee for Bristol-Myers Squibb.

Dr. Crowther discloses that he received grant monies from the Heart and Stroke Foundation, the Canadian Institutes for Health Research, Leo Laboratories, Pfizer, and Sanofi-Aventis. He also received consultant fees from Leo Laboratories, Sanofi-Aventis, Bayer, and Pfizer. Dr. Crowther has served on the speakers bureau for Leo Laboratories, Pfizer, Bayer, and Organon, and is on an advisory committee for Bayer.

Dr. Palareti discloses that he serves on the speakers bureau of Sanofi-Aventis, GlaxoSmithKline, Instrumentation Laboratory of Roche Diagnostics, and Dade-Behring. He is a member of the Executive Committee of the Italian Federation of Anticoagulation Clinics and the Italian Society of Hematology and Thrombosis (ISTH), and is Co-chair of the Subcommittee on Control of Anticoagulation of the ISTH.

ENDORSER(S)

American College of Clinical Pharmacy - Medical Specialty Society
American Society of Health-System Pharmacists - Professional Association

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K

antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004 Sep;126(3 Suppl):204S-33S.

GUIDELINE AVAILABILITY

Electronic copies: Available to subscribers of the Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

Executive Summary:

- Antithrombotic and thrombolytic therapy executive summary. Chest 2008 Jun; 133:71S-109S.

Background Articles:

- Antithrombotic and thrombolytic therapy. Chest 2008 Jun; 133:110S-112S.
- Methodology for antithrombotic and thrombolytic therapy guideline development. Chest 2008 Jun; 133:113S-122S.
- Grades of recommendation for antithrombotic agents. Chest 2008 Jun; 133:123S-131S.
- Strategies for incorporating resource allocation and economic considerations. Chest 2008 Jun; 133:132S-140S.

Electronic copies: Available to subscribers of the Chest - The Cardiopulmonary and Critical Care Journal.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on November 19, 2004. The information was verified by the guideline developer on January 12, 2005. This summary was updated by ECRI on December 7, 2005 following the U.S. Food and Drug Administration (FDA) advisory on NovoSeven. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug

Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute on November 24, 2008. The updated information was verified by the guideline developer on January 7, 2009.

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Date Modified: 2/16/2009


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